The value of abdominal ultrasonography compared to colonoscopy and faecal calprotectin in following up paediatric patients with ulcerative colitis

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Abstract

Aim: To evaluate the value of abdominal ultrasonography (US) in the follow-up of paediatric patients with ulcerative colitis (UC) compared to faecal calprotectin (FC) and colonoscopy. **Material and method:** In this retrospective study we enrolled 30 paediatric patients previously diagnosed with UC, examined by abdominal US and colonoscopy within the same week. FC was also determined during the same week. Disease activity was established using the paediatric ulcerative colitis activity index (PUCAI). The global endoscopic activity was evaluated using the Mayo endoscopic subscore. **Results:** Endoscopy revealed pathological findings of active disease in 27 out of 30 patients; 3 patients were in endoscopic remission. Only 18 of them had clinical active disease (PUCAI >10), [sensitivity (Se) 66.7% and specificity (Sp) 33% of PUCAI in detecting endoscopic active disease). Twenty-three (76.7%) patients had FC >250 mcg/g, but in 2 of these cases the colonoscopy was normal (Se 77.8% and Sp 33.3% in detecting active disease). At US examination, pathological findings (increased bowel wall thickness, hypervascularity, lymphadenopathies, and/or mesenteric inflammatory fat) were found in 27 patients (90%), all with endoscopic active disease (agreement US - colonoscopy, at patient level, $k=1.0$, $p<0.001$, Se 100% and Sp 100%). At segment level (totally 180 bowel segments examined by US), the overall agreement between US and colonoscopy was $k=0.767$, $p<0.001$, Se 86.5%, Sp 90.1%. Of the 27 patients with US pathological findings in any of colonic segments, 23 had FC >250 mcg/g (85.1%). The inter-observer agreement for the US measurements had an overall ICC of 0.926 with $p<0.001$. **Conclusion:** Abdominal US findings demonstrate a good to excellent concordance with endoscopic examination and are correlated with elevated FC levels. Therefore, US appears as an accurate technique in assessing activity in patients with UC and might replace colonoscopic evaluation for the follow-up.

Keywords: ultrasonography; colonoscopy; faecal calprotectin; IBD; ulcerative colitis

Introduction

Paediatric inflammatory bowel disease (IBD), with the two main entities, Crohn's disease (CD) and ulcerative colitis (UC), is a chronic, relapsing inflammatory condition of the gastrointestinal tract, with a worldwide

increasing prevalence [1-3] and a major long-term implication in the patient's growth, pubertal development and the quality of life [4].

Children with UC commonly present with abdominal pain, diarrhoea and rectal bleeding [5,6], but extraintestinal manifestations (6 to 17% of the patients [7,8]) including arthritis, uveitis or liver and colorectal carcinoma [9,10] can also be detected.

The European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) revised Porto criteria [11] for UC diagnosis include typical clinical manifestations and the confirmation of chronic active inflammation by colonoscopy (classically, starting from

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rectum with ascending progression in a continuous manner with no small bowel involvement) with multiple biopsies. Typical endoscopic findings are represented by erythematous, bleeding, friable, erosive, ulcerative mucosa and loss of vascularity [11,12]. The microscopic features of UC are represented by active (neutrophils infiltration) and chronic inflammation (modified architecture of the crypts and lymphoplasmacytic infiltrates) [11,13,14].

The disease activity is currently assessed using the paediatric ulcerative colitis activity index (PUCAI), colonoscopy with multiple biopsies and faecal calprotectin (FC). Colonoscopy with biopsies is the gold standard for IBD diagnosis [15]. The recent ESPGHAN and European Crohn's and Colitis Organisation (ECCO) guidelines recommend colonoscopic evaluation not only for the diagnosis but also for follow-up and assessment of therapeutic response (when major changes in treatment are necessary, cancer surveillance, when FC is elevated, but the symptoms are not clearly disease-related, and in patients with sustained clinical remission with high level of FC) [9]. The main limitations of endoscopy are the need of general anaesthesia and the possible complications, such as gastrointestinal bleeding and perforation [16,17]. Colonoscopy is not easily accepted by children and their caregivers, especially the repeated procedures, performed just to confirm the mucosal healing.

FC represents a non-invasive marker of inflammation [18]. No ideal cut-off value of FC has been yet established [19,20] but according to ESPGHAN revised Porto criteria in children and adolescents [11], a value above 250 µg/g reflects more accurately the mucosal inflammation, with sensitivity (Se), specificity (Sp), positive predictive value (PPV) and negative predictive value (NPV) of 71%, 100%, 100% and 47.1%, respectively [21].

Among the imaging techniques, Magnetic Resonance Enterography (MRE) has high accuracy in identifying the bowel wall modifications and the disease complications [11,22]. However, high-quality images in children are more difficult to be obtained when compared to adults [23], due to the movement artefacts, poor acceptance of the oral contrast and the need of general anaesthesia [24]. The low accessibility, long examination time, need for specific radiological competence and high cost are other limits of this method [25,26].

Abdominal ultrasound (US) is a non-invasive, low cost, accessible, reproducible and easily accepted by children imaging technique, used more and more frequently in the recent years in assessing bowel inflammation [27,28]. It is largely used in clinical practice for abdominal complaints or check-up examinations. US was found to have 79.7% sensitivity and 96.7% specificity

[29] in assessing the extension and activity of IBD [30], with a good concordance with the MRE findings [23,31]. In a recent systematic review in pediatric IBD, van Wassenae et al [30] concluded that the increased bowel wall thickness (BWT), bowel wall vascularization, presence of enlarged lymph nodes, alteration of wall stratification, creeping fat, abscesses or other complications and the absence of colonic haustration were the major US criteria for IBD. The majority of the included studies regarded both UC and CD patients (with a smaller number of UC), or only CD patients. Therefore, data about the usefulness of US in paediatric UC are limited [32]. Moreover, monitoring IBD patients using US is not yet part of the routine standardized clinical practice, despite the good results of published studies, in both children and adults [33-37].

Given these reasons, our aim was to analyse the value of US in following up UC paediatric patients, compared to FC and colonoscopy.

Material and methods

This was a retrospective study, approved by the local Ethics Committee. Written informed consent was signed by the patient's legal tutors before investigations, according to the hospital protocol.

Study Population

From the hospital database, we selected the paediatric patients previously diagnosed with UC, according to the revised Porto criteria [11]. Patients were examined during admission by abdominal US and colonoscopy, within the same week, between January 2018 and January 2020. We excluded from the study the patients that did not provide a faecal sample. Patients without a legal tutor on admission were also excluded. Disease location and phenotype were determined using the Paris Classification of IBD [38] and data about the medications were collected.

Faecal calprotectin

All patients provided a faecal sample, stored at 4°C until processed [19], for the FC determination using ELISA.

Abdominal US

The protocol of the hospital regarding the abdominal US in IBD patients includes a standard preparation, patients being advised to fast for at least 8 hours. All the US examinations were performed by one of the two paediatric radiologists with more than 10 years of experience in bowel US, using Xario™ 200 (Cannon Medical Systems Corporation, Otawara, Japan) or Aplio 500 machine (Canon Medical Systems Corporation, Otawara, Japan) with linear (7-14 MHz) and convex (4-6 MHz) transducers, without oral contrast medium administration. The investigation protocol included systematic evaluation

Fig 1. Normal aspect of the bowel segments: a) longitudinal scan of the terminal ileum; b) transverse scan of the ascending colon; c) longitudinal scan of the transverse colon; d) longitudinal scan of the descending colon; e) transverse aspect of the sigmoid; f) longitudinal scan of the rectum (measurements in all cases between callipers).

of the abdomen starting with the intra-abdominal solid organs using a low frequency convex probe, with the patient lying supine [27]. For a better examination of the large bowel, the high frequency linear probe [39] with graded compression [40] was used, starting at the caecum in the right iliac fossa, after the localization of the terminal ileum and progressing distally for the evaluation of ascending, transverse, descending and sigmoid colon [27]. Representative images from each bowel segment, normal or pathological (fig 1 and 2), were stored in each case in the Picture Archiving Communication System (PACS), as the standard protocol of our hospital requires.

The images stored in PACS were analysed individually by the two radiologists, blinded to the result of the colonoscopy, value of FC and PUCAI. In all bowel segments the following parameters were evaluated: BWT (normal value <3 mm for all segments), bowel vascularity (using power Doppler), presence of lymphadenopathies and mesenteric inflammatory fat, following the published protocols [27,41]. In case of disagreement between the examiners, the images were reviewed and

conclusion was reached by consensus. The disease activity for each bowel segment on US was classified as present/absent based on the radiologist's comprehensive examination.

Colonoscopy

All endoscopic evaluations were performed using paediatrics OLYMPUS CV-190 (Hamburg, Germany) endoscopes. All patients underwent bowel preparation with osmotic laxative, the afternoon before the colonoscopy [42]. On the day of examination, only clear liquids were permitted. The colonoscopy procedure and the assessment of inflammation, disease localization (rectum, sigmoid colon, descending colon, transverse, ascending colon, caecum and terminal ileum), severity and complications were documented using a standardized worksheet by a paediatric gastroenterologist with more than 10 years of experience. The global endoscopic activity was evaluated using the Mayo endoscopic subscore [43] (0 – normal/inactive, 1 – mild, 2 – moderate and 3 – severe disease) and the result was recorded immediately after the procedure.

Fig 2. Pathological aspect of the colon: a) transverse scan of the ascending colon, color Doppler ultrasound – the walls are thickened and hypervascularized; b) transverse scan of the proximal descending colon with increase bowel wall thickness; c) longitudinal scan of the distal descending colon with increase bowel wall thickness; d) mesenteric inflammatory lymphadenopathies. Of note the increased thickness and echogenicity of the submucosal layer.

Statistical analysis

The Shapiro-Wilks test was used to assess the distribution of continuous variable. Descriptive analysis was performed and the results were presented as number (percent) for categorical variables and median (interquartile range) for continuous variables – all being non-normally distributed. The differences of medians between more than two independent samples were assessed using the Independent Samples – Kruskal-Wallis test. The agreement between the diagnosis methods of disease activity was measured by calculating the Cohen's kappa coefficients (k). Cohen's k values were interpreted as follows: < 0 no agreement, 0–0.20 poor, 0.21–0.40 fair, 0.41–0.60 moderate, 0.61–0.80 good, and 0.81–1 very good agreement. The sensitivity (Se) and specificity (Sp) for each method were also calculated, considering endoscopy as gold standard for disease activity. The intraclass correlation coefficient (ICC) was calculated to assess the overall inter-observer agreement for the US measurements. The ICC value was interpreted as poor when less than 0.50, moderate between 0.50 and 0.75, good between 0.75 and 0.90, and excellent when greater than 0.90. A p-value less than 0.05 was considered statistically significant. IMB SPSS Statistics v.23 and Microsoft Office 365 Excel were used to perform the statistical analysis.

Results

A total number of 30 children previously diagnosed with UC were selected from the hospital database. Patients' baseline characteristics are shown in Table I.

Of the 30 patients included in study, 27 (90%) had active lesions at colonoscopy, but only 18 of the 27 had clinical active disease with PUCAI >10, (Se 66.7%, Sp 33% of PUCAI in detecting active disease). FC >250 mcg/g was found in 23 (76.7%) patients, but in 2 of these cases the colonoscopy was normal (Se 77.8%, Sp 33.3% of FC in identifying the active disease).

At US, pathological findings were found in 27 patients, all with endoscopic active disease (excellent agreement between US and colonoscopy, at patient level, $k=1.0$, $p<0.001$, Se=100%, Sp=100%). When the results were analysed on a segment level (totally 180 bowel segments evaluated by US), the overall agreement between US and colonoscopy was good ($k=0.767$, $p<0.001$, Se 86.5%, Sp 90.1%) (details in Table II). Of the 27 patients with US pathological findings in any of colonic segments, 23 had FC >250 mcg/g (85.1%).

The overall inter-observer agreement for the US measurements was excellent (ICC=0.926, $p<0.001$).

Analysing the discordances between US and colonoscopy, we found that US detected normal findings, as

Table I. Patients' baseline characteristics

Patient baseline characteristics (N=30)	
Age (years)	12.3 (8.4-16.45)
Sex (males)	22 (73)
Disease localization at diagnosis/study inclusion	
Proctitis	10 (33.3)/9 (30)
Left-sided colitis	15 (50) /13 (43.3)
Pancolitis	5 (16.6)/8 (26.6)
Disease duration (years)	2.68 (0.5-3.7)
Mayo endoscopic subscore	
0	3 (10)
1	10 (33.3)
2	15 (50)
3	2 (6.6)
Clinical activity (PUCAI)	
Inactive (<10)	10 (33.3)
Mild (10-34)	14 (46.6)
Moderate (35-64)	6 (20)
Severe (>65)	0 (0)
Medication*	
5-ASA	27 (90)
Steroids	11 (36.6)
Azathioprine	1 (3.3)
FC (mcg/g)	300.0 (246.5-700.0)

Results are expressed as number (%) or as median (interquartile range); Mayo endoscopic subscore: 0 – normal/inactive, 1 – mild, 2 – moderate and 3 – severe disease; PUCAI: pediatric ulcerative colitis activity index; FC: faecal calprotectin; * more than one type of medication possible in any patient

follows: in one rectum, 4 sigmoid colon, 4 descending colon, 2 transverse colon and one ascending colon segments, all with colonoscopy inflammatory signs. In 2 descending colon, 2 transverse colon and 2 ascending colon segments US detected increased BWT despite the normal colonoscopic aspect.

The differences between the medians of the BWT of each bowel segment according to the Mayo endoscopic subscore are listed in Table III. Lymphadenopathies, bowel hypervascularisation and mesenteric inflammatory fat were detected in all patients with Mayo endoscopic subscore 3, whereas only 7 patients (46.6%) with Mayo subscore 2 presented hypervascularity and adenopathies, with no mesenteric inflammatory fat at US.

Discussion

In this retrospective study, we assessed the value of US in evaluating UC paediatric patients during follow-up, compared to FC and colonoscopy. We found that US was able to identify all patients with endoscopic active

Table II. Ultrasound and colonoscopy agreement for each bowel segment

Segment	Ultrasound	Colonoscopy	k	P	Se (%)	Sp (%)
Rectum	25 (83.3)	26 (86.7)	0.870	<0.001	96.2	100
Sigmoid colon	22 (73.3)	26 (86.7)	0.595	<0.001	84.6	100
Descending colon	15 (50.0)	17 (56.7)	0.600	0.001	76.5	84.6
Transverse colon	10 (33.3)	10 (33.3)	0.700	<0.001	80.0	90.0
Ascending colon	9 (30.0)	8 (26.7)	0.754	<0.001	87.5	90.9

Results are expressed as number (%); Se: sensibility; Sp: specificity; k: < 0 no agreement, 0–0.20 poor, 0.21–0.40 fair, 0.41–0.60 moderate, 0.61–0.80 good, and 0.81–1 very good agreement; p< 0.05: statistically significant.

Table III. Mayo endoscopic subscore and median of the bowel wall thickness for each bowel segment

	Median BWT at US				p
Mayo Score	0	1	2	3	
Bowel segment					
Rectum	2.3 (2.3-2.45)	3.45 (3.0-4.0)	4.0 (3.1-4.75)	3.65 (3.3-4.0)	0.043
Sigmoid colon	2.2 (2.2-2.35)	3.3 (2.5-3.8)	4.0 (3.3-4.75)	3.95 (3.4-4.5)	0.031
Descending colon	2.2 (2.1-2.2)	2.65 (2.5-3.8)	3.3 (2.5-4.25)	3.6 (3.5-3.7)	0.067
Transverse colon	2.4 (2.4-2.55)	2.6 (2.4-3.1)	2.5 (2.35-3.15)	3.15 (2.1-4.2)	0.978
Ascending colon	2.6 (2.3-2.7)	2.45 (2.3-3.5)	2.3 (2.2-2.9)	2.85 (2.2-3.5)	0.693

Results are expressed as median (range); BWT: bowel wall thickness; US: ultrasound; p< 0.05: statistically significant.

disease, at patient level, but there were some differences between the identification of the affected bowel segments by the two aforementioned methods. The discordances between US and colonoscopy may occur, as described in the study of Christensen et al [44], taking into account that the mucosal healing is not in all cases uniform, proximal to distal, but also in a patchy manner. Moreover, US has the potential to examine all the layers of the bowel wall and the extraintestinal features, whereas colonoscopy is limited to the visualisation of the intestinal mucosa.

The US is recognised as first line imaging technique in assessing patients with IBD [45,46]. Generally, B-mode US and Doppler techniques are used and, in the last years, elastography; the oral contrast is useful only for small bowel investigation and intravenous contrast has not been approved for paediatric population. The performance of US in IBD paediatric patients was evaluated in many studies, by comparing this method to colonoscopy, histology or MRE. Barber et al [23] found in CD paediatric patients a good concordance between US and MRE findings, regarding the disease activity and localisation. These authors demonstrated also high specificity (the highest for sigmoid colon) of both imaging techniques in identifying the active disease and the histology confirmed disease at bowel segment level. A significant learning curve was demonstrated for MRE, with improvement of the results after 10 examinations, but not for US. This suggests that, for experienced radiologists, both methods can be used for follow-up. The same good agreement between US and MRE was

obtained by Dillman et al [47] in children with CD. In this retrospective study, the interobserver agreement was best for the maximum BWT (95%CI 0.67 [0.64-0.70]) and relatively weak for the length of involved segment (95%CI 0.41 [0.35-0.40]). In our UC patients, we found an excellent agreement between radiologists, concerning the measurement of the BWT. The discrepancy with the aforementioned study could be related mainly to the underlying disease. While in CD the bowel is inflamed in a discontinuous and inhomogeneous manner (requiring the choice of the same segment for measurement in order to have a good interobserver agreement), in UC the disease is continuous and involves the entire circumference of the colon.

IBD cases may present different evolutive trends [48]; therefore, these patients must be monitored for long periods. The disease can progress to more extensive forms, more frequently in paediatric patients compared to adults (29.2 % vs 20.2%) [48]. In our study, 5 children were diagnosed with pancolitis at onset and, during the follow-up, 3 other patients were found to have pancolitis at colonoscopy. US correctly identified all these three cases. Due to the good agreement between US and colonoscopy findings on patient and on segment level, we concluded that US can be used not only for assessing the favourable evolution of the disease but also to identify flares and to establish the new extension of UC. This is of utmost importance, as in these cases the colonoscopy could be replaced by US, much easier accepted by children and/or parents.

Mucosal healing or endoscopic remission is the ideal target for nowadays disease management strategy [49]. Clinical remission is considered when PUCAI <10 [50], but approximately 20% of children in Turner et al [9] and over 50% of children in Sarbagili-Shabat et al studies [51] had endoscopic inflammation despite clinical inactive disease. This category of patients, being asymptomatic and probably with normal FC, cannot undergo colonoscopy examination at every follow up visit. In these cases, US can bring important information about the condition of the colonic wall.

Kellar et al [52] developed a US activity score - the simple paediatric ultrasound score (SPAUSS) - in order to determine the most reliable parameter (mesenteric inflammatory fat, mesenteric lymph nodes, hyperemia/Doppler color flow and BWT) to predict bowel inflammation. Out of these 4 parameters, BWT and mesenteric inflammatory fat had significant prediction value for the severity of the disease. In our study, all the children with Mayo subscore of 3 presented mesenteric inflammatory fat and BWT >3 mm in all analysed segments.

No definition/recommendation about US findings regarding the remission in UC was published. However, as US can detect almost all the bowel segments, assess the inflammation, measure the BWT and has good correlation with colonoscopy findings, PUCAI and FC, the technique has to be considered for future analysis of IBD in children. US should be regarded as a valuable imaging technique for UC evaluation.

The main limitations of our study are the retrospective design, heterogeneity and the low number of patients. In addition, we did not compare the US findings, especially the power Doppler signal with the histology results. The lack of comparison of the US aspect with other imaging techniques, especially, MRE, is another limit of our study. It would have been of interest to compare US data at diagnosis and at the inclusion in the study, but due to lack of information regarding the US data at the diagnosis in some patients, we could not realize this analysis. Due to the retrospective design of our study, we did not analyse whether the US findings should prompt the clinician to reconsider the treatment options.

Conclusion

In conclusion, due to the good to excellent agreement between abdominal US and colonoscopy findings on patient and bowel segment levels, US should be considered as a useful imaging technique to assess and follow-up UC patients. The good correlation between elevated FC level and pathological US findings confirms the value of US in detecting bowel inflammatory process. US might

replace the colonoscopy evaluation on follow-up, especially when PUCAI and FC suggest active disease.

Conflict of interest: none

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